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SimCardioTest - Simulation of Cardiac Devices & Drugs for in-silico Testing and Certification

Technical Report
D1.1: Modelling & Personalisation Survey

Work Package 1 (WP 1)
Model Standardisation & Interoperability

Task Lead: SRL, Norway
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DELIVERABLE INFORMATION

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EXECUTIVE SUMMARY

The document is part of the WP1 on Model Standardisation & Interoperability and presents survey response on the different pipelines that will be implemented in the Use Cases and summarises the technical requirements for the different software that will be used. It is based on information provided by all partners through surveys and meetings.

ACRONYMS

- CEPS: Cardiac electrophysiology solver software
- CHUB: Centre Hospital Universitaire de Bordeaux
- CT: computed tomography
- Inria: INSTITUT NATIONAL DE RECHERCHE EN INFORMATIQUE ET AUTOMATIQUE
- InSiLAAO: In silico clinical trial for LAAO devices
- LAA: left atrial appendage
- LAAO: Left atrial appendage occluder
- MPC: MICROPORT SORIN
- MRI: Magnetic Resonance Images
- Sofa: Simulation Open Framework Architecture software
- UBx: Université de Bordeaux
- UPV: Universitat Politecnica de Valencia

1. Introduction

The overall goal of the SimCardioTest project is to advance the use of computer simulations in the development and testing of devices and drugs that can be used to alleviate a variety of cardiac diseases. One of the final products of this project will be a web-based platform that can be used to test cardiac devices and drugs in 3 specific Use Cases. We will focus on 3 specific use cases wherein the modeling pipeline and simulation software are already quite advanced. The first challenge is to standardize the approach for each pipeline. In this deliverable, we will provide a summary of the tentative workflow pipelines for each Use Case and the technical requirements for the different software that will be used. For each of the pipeline, we divide the flow into the pre-processing steps which will be performed outside of the platform, input to the platform, the simulations or actions that will be done within the platform, and the output. The information presented here has been provided by all partners through surveys and meetings held within the first 6 months of project start and are available in the Appendix: Software Technical Survey Results (pp9-22).

2. Use Case Pipeline Survey Results

2.1 Use Case 1: Pacing leads and catheters

Cardiac resynchronization therapy restores the normal sequence of activation in the heart using a stimulator that activates pacing leads implanted at different sites throughout the atria and ventricles. Current technologies have made it possible to create ultra-thin catheters that increases the possible sites that the lead can be navigated to. This flexibility has the potential to increase the effectiveness of this therapy. However, some major design challenge with these leads is the challenge of navigating the leads through the cardiac vasculature, testing their ability to electrically capture cardiac tissue, and the mechanical stability of the implanted lead. Use Case will investigate these 3 different applications.

Pipeline 1: Testing of interventional navigation
Platform Goal: Interactive navigation of ultra-thin catheters through patient-specific vasculature.

1. Pre-processing: Cardiac CT scans selected from data source provided by Centre Hospital Universitaire de Bordeaux (CHUB)
2. Pre-processing: CT scans transferred from CHUB to UBx
3. Pre-processing: Cardiac vessels segmented and meshed by UBx
4. Input: Masks / meshes transferred from UBx to Inria
5. Input: Device characteristics transferred from MPC to Inria
6. Platform task: Navigation simulated by Inria using SOFA

Pipeline 2: Quantification of stimulation capture
Platform Goal: Determine if in silico prototype of microelectrode can effectively pace cardiac tissue

1. Pre-processing: Detailed anatomy acquired (microCT, high-field MRI) obtained by UBx
2. Pre-processing: Image processing and meshing using MUSICardio (UBx)
3. Input: Anatomical mesh
4. Input: Pacing device and stimulation characteristics provided by MPC

5. Platform task: Simulation of capture using CEPS developed by UBx
6. Output: Report on device success/failure in stimulating tissue

Pipeline 3: Prediction of pacing lead fatigue and rupture
Platform Goal: Determine mechanical stability of implanted lead

1. Input: Experimental data on mechanical behavior of the lead
2. Input: Previously generated cardiac meshes with material properties
3. Platform task: Mechanical simulation using SOFA (Inria)
4. Output: Report on fatigue quantification (mechanical parameters, deformed geometry, distribution of curvature and effort per lead section, stress) and tissue rupture limits

2.2 Use Case 2: Left atrial appendage occluders

The left atrial appendage (LAA) is a sac like structure located on the left atria. Certain LAA geometries can lead to blood flow stagnation that can promote formation of clot. This clot can then rapture and cause stroke. To prevent this event from happening, LAA occluders can be implanted to completely isolate the LAA. The goal of Use Case 2 is to identify patients that will benefit from LAA occlude implantation.

Pipeline 1: LAAO patient selection
Platform Goal: Stratify the risk of clot formation in patient's LAA

1. Pre-processing: A library of simulations of LAAO cases will be generated from previously obtained left atrial anatomies and LAAO geometries provided by Boston Scientific. Simulations will be performed using Oasis software developed in Simula.
2. Input: Patient(s) of interest LA mesh obtained from patient CT scan
3. Platform task: For each test case, find the nearest match from the virtual library (**InSiLAAO**).
4. Output: Report predicting the patient response to LAAO implantation.

2.3 Use Case 3: Drug efficacy and cardiotoxicity

Drug efficacy and cardiotoxicity tests are an expensive step in the drug development pipeline. Additionally, the drug response can vary among the population due to differences in demographic characteristics or underlying disease states. For Use Case 3, the goal is to provide a virtual test for drugs of interests and analyze their efficacy and safety in different populations.

Pipeline 1: Testing of drug safety and efficacy
Platform Goal: Simulate drug safety and efficacy

1. Input: Drug binding properties obtained from literature or pharmaceutical company
2. Input: Population of interest (user define sampling of age, sex, weight, disease state, etc.)
3. Platform task: Dose response for target population will be performed using **ExactCure** software
4. Platform task: 0D electrophysiological simulations for target population on electrophysiological response using **MATLAB** code generated by UPV
5. Platform task: 3D electrophysiological simulations on selected cardiac geometries performed using **ELVIRA** software developed by UPV

6. Platform task: 3D electromechanical simulations on slabs to determine effects on conduction and contraction will be simulated using **FEniCS-pulse** software developed by Simula
7. Output: Report on drug safety and efficacy on virtual population response

3. Conclusion

This report contains the most current design of the Use Case pipelines as envisioned in the SimCardioTest proposal. The results in this survey will be used to identify technical challenges in implementing these complex workflows that require the integration of different software and in some cases simulation environments. The pipelines will be further refined and the underlying software will be standardized in order to make inputs and outputs of each pipeline compatible with each other. This will eventually lead to a unified pipeline that will increase the utility of the virtual platform by allowing unique studies that can investigate more complex scenarios such as drug-device interactions. The results of the standardization efforts will be reported on month 12 of the project timeline.

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Appendix: Software Technical Survey Results

Appendix 1 SOFA (Inria)

Product Name: SOFA

Description: Software for simulation of mechanical activity

IP Ownership: INRIA

Development phase:

□ Discovery □ Preclinical □ Clinical □ Post-launch

Typical user workflow (describe what the user will do, step by step, to use your tool):

Input: parameter text file describing meshes (both cardiac and electrode), material properties, solvers to use, boundary conditions, etc.

Output: results can be visualized via paraview or through an automatically generated report

Therapeutic area: Simulation of mechanical interaction between heart and device

Documentation:

□ Publication/Validation:

□ Webinar:

□ Other: https://www.sofa-framework.org/

Software requirements (scripting language, libraries, tools): …

- Open C++ core

https://github.com/sofa-framework (Open source license: GNU LGPL 2.1)

- cmake > 3.10.1
- openMPI > 4.0.1
- Eigen 3.3.7
- Petsc > 3.2
- ParMetis 4.0.3 or PtScotch 6.0.6
- VTK > 8.2.0

System and computing requirements (operative system, launch batch mode, single-/multi-threading): …

Can run on Linux, MacOS, Windows, etc.

Simulations can be run in batch mode

Single or multi-thread

Tool Files (number of files, type, format, size, etc.) - files needed to run the model:

Tool summary:

Input parameters: ¨ <5 ¨5<X<10 x X>10

Simulation types: ¨ 1 z X>1

Dataset Files (number of files, type, format, etc.) - in case your tool includes a dataset:

Dataset summary:

Size:

Number of variables:

Number of records:

Targeted end-user:

¨ Beginner

¨ Researcher ¨ Clinician ¨ Regulator ¨ Industry

Appendix 2: CEPS (UBx)

Product Name: CEPS

Description: Simulation software of cardiac electrophysiology. Computes propagation of action potentials.

IP Ownership:	Inria, Université de Bordeaux, Institut Polytechnique de Bordeaux, CNRS

Development phase:

X Discovery □ Preclinical □ Clinical □ Post-launch

Typical user workflow (describe what the user will do, step by step, to use your tool):

- Build/get meshes,
- write short text input file, specific input data will be defined for the project
- run simulation,
- view results, paraview or other, other types of output will be defined during the project

Therapeutic area: Electrophysiology, pacing, ablations

Documentation:

□ Publication/Validation:

□ Webinar:

□ Other: https://carmen.gitlabpages.inria.fr/ceps/

Software requirements (scripting language, libraries, tools):

- c++ compiler
- cmake > 3.10.1
- openMPI > 4.0.1
- Eigen 3.3.7
- Petsc > 3.2
- ParMetis 4.0.3 or PtScotch 6.0.6
- VTK > 8.2.0

System and computing requirements (operative system, launch batch mode, single-/multi-threading): …

- Continuous integration with Ubuntu latest, CentOS. Usually run in batch mode using MPI for parallel computing (just MPI, no threads)

Tool Files (number of files, type, format, size, etc.) - files needed to run the model:

- Input :
  - mesh(es) (.vtk or .msh or .mesh) with or without data on fiber orientation, region attributes.
  - parameter file (text file)

- Output :
  - Parallel vtk or pvtu files + xml collection files, showing action potential + activation maps.
  - any additional output data that will be needed for the project

Tool summary:

Input parameters: X>10

Simulation types: X>1

Dataset Files (number of files, type, format, etc.) - in case your tool includes a dataset:

Dataset summary:

Size:

Number of variables:

Number of records:

Targeted end-user:

¨ Beginner

X Researcher ¨ Clinician ¨ Regulator ¨ Industry

Appendix 3: InSiLAAO (UPF)

Product Name: InSiLAAO

Description: In silico clinical trial for LAAO devices from corresponding use case in SimCardioTest EU project

IP Ownership: UPF

Development phase:

X Discovery □ Preclinical. □ Clinical □ Post-launch

Typical user workflow (describe what the user will do, step by step, to use your tool):

User upload CT images of left atria of a given number of patients and information about the LAAO device that was implanted (type and size); the upload can be an excel-like file with a path where the CT image is and device configuration (other patient information can be included, such as demographics, etc); the user executes the pipeline in the Cluster (UPF), where DL-based automatic segmentation will be performed, then morphological characterization to find the closest case in the already generated virtual library (> 100 cases); in the virtual library, several fluid simulations will be available for each virtual case, with different device settings (type, size, positioning); a report will be provided for each analysed case showing haemodynamic indices from the closest virtual case, together with the similarity between the real and virtual case, and the risk of adverse events.

Therapeutic area:

Interventional cardiology, specifically the optimization of left atrial appendage occluder devices that are implanted in atrial fibrillation patients with contra-indications to oral anti-coagulants.

Documentation:

X Publication/Validation:

□ Webinar:

□ Other:

Software requirements (scripting language, libraries, tools):

Simulations will be run at the UPF cluster. Connection with Dockers for medical image segmentation will be necessary. The front-end could be quite simple, only showing reports for patients with numerical values, 2D plots and graphs. Individual fluid simulations on the virtual library could be visualized if connecting with the VIDAA platform developed at UPF, for which a call from the in silico trial platform would be needed.

System and computing requirements (operative system, launch batch mode, single-/multi-threading): …

Tool Files (number of files, type, format, size, etc.) - files needed to run the model:

Tool summary:

Input parameters: ¨ <5 X 5<X<10 ¨ X>10

Simulation types: X 1 ¨ X>1

Dataset Files (number of files, type, format, etc.) - in case your tool includes a dataset:

The input would be Computerized Tomography (CT) scans, from 100 to 200 (up to 200 maximum), together with available patient information. Paths for CT scans and the remaining information could be stored in a excel-type file.

Dataset summary:

Size:

Number of variables:

Number of records:

Targeted end-user:

¨ Beginner

¨ Researcher X Clinician ¨ Regulator X Industry

Appendix 4: ExactCure

Product Name: ExactCure

Description: simulate the concentration of drug in the blood of the patient, taking into account his/her personal characteristics.

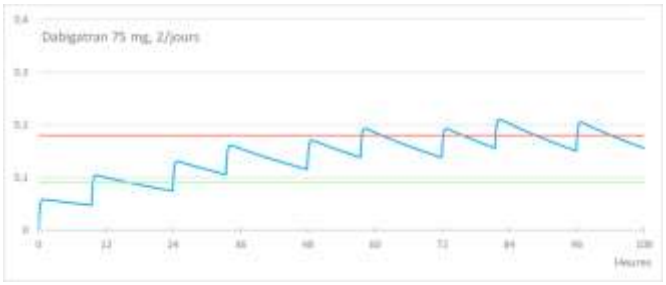
IP Ownership: ExactCure

Development phase: N/A

□ Discovery □ Preclinical □ Clinical □ Post-launch

Typical user workflow (describe what the user will do, step by step, to use your tool):

1. **The user enters the name & dosage of the drug he wants to simulate + patient's characteristics.**
2. **He gets a simulation back (image and/or data file with Cmax, half-life, tbd).**



Therapeutic area: cardiovascular for SimCardioTest

Documentation: N/A

□ Publication/Validation:

□ Webinar:

□ Other:

Software requirements (scripting language, libraries, tools): N/A

System and computing requirements (operative system, launch batch mode, single-/multi-threading): …

N/A

Tool Files (number of files, type, format, size, etc.) - files needed to run the model:

1 input file (JSON) from InSilicoTrial to ExactCure. Very small, just a few parameters.

No direct result back from ExactCure to InSilicoTrials.

Tool summary:

Input parameters: <5 þ 5<X<10 X>10

Simulation types: 1 X>1

Dataset Files (number of files, type, format, etc.) - in case your tool includes a dataset:

N/A

Dataset summary:

Size:

Number of variables:

Number of records:

Targeted end-user:

Beginner

þ Researcher þ Clinician Regulator þ Industry

Area's expected impact:

Appendix 5: Drug safety and efficacy assessment in cellular models (UPV)

Product Name: Drug safety and efficacy asessment in cellular models
Description: Cellular simulations of drug effects

IP Ownership:
UPV

Development phase:	
X□ Discovery	X□ Clinical
X□ Preclinical	X□ Post-launch

Therapeutic area:
Safety for any drug compound selection in preclinical screening,
Efficacy for cardiac pathologies

Documentation:
X□ Publication/Validation:
Romero, L., Cano, J., Gomis-Tena, J., Trenor, B., Sanz, F., Pastor, M., & Saiz, J. (2018). In Silico QT and APD Prolongation Assay for Early Screening of Drug-Induced Proarrhythmic Risk. Journal of Chemical Information and Modeling. https:// doi.org/10.1021/acs.jcim.7b00440
□ Webinar:
□ Other:

Software requirements (scripting language, libraries, tools): Matlab

System and computing requirements (operative system, launch batch mode, single-/multi-threading):
Windows or Linux

Tool File(s):

Tool summary:
Input parameters: ¨ <5 ¨ 5<X<10 X¨ X>10
Simulation types: ¨ 1 X¨ X>1

Data File(s): matlab files with input data

Dataset summary:

Size:

Number variables: ~X

…

Number records: ~X

…

Targeted end-user:

¨ Beginner

X¨ Researcher ¨ Clinician ¨ Regulator X¨ Industry

Area's expected impact:

Appendix 6: ELVIRA (UPV)

Product Name: Drug safety and efficacy asessment in 3D models

Description: Simulations of drug effects in 3D electrophysiological and mechanical models

IP Ownership:
UPV

Development phase:	
X□ Discovery X□ Preclinical	X□ Clinical X□ Post-launch

Therapeutic area: Safety for any drug, Efficacy for cardiac pathologies.

Documentation:

□ Publication/Validation:

□ Webinar:

□ Other:

Software requirements (scripting language, libraries, tools):

Simulations will be ran in our cluster. The platform will serve as an interface connected to our clusters (linux).

Linux.

Launch batch mode: with Bash scripting

Sinle and multi threading.

System and computing requirements (operative system, launch batch mode, single-/multi-threading):

The Ci2B possesses its own cluster dedicated to running simulations at all scales (0D cell, 1D fiber, 2D tissue and whole 3D organ). The cluster incudes 37 multi-core nodes. The number of cores available at each node varies between 4 and 272, depending on the purpose of the node (0D, 1D, 2D or 3D simulations).

Tool File(s):

Tool summary:

Input parameters: ¨ <5 ¨ 5<X<10 X¨ X>10

Simulation types: ¨ 1 X¨ X>1
Data File(s):
Dataset summary: Size: Number variables: ~X … Number records: ~X …
Targeted end-user: ¨ Beginner x¨ Researcher ¨ Clinician ¨ Regulator x¨ Industry

Appendix 7: FEniCS-pulse (Simula)

Product Name: FEniCS-pulse

Description: Cardiac Electromechanical Simulator

IP Ownership: Simula (open source)

Development phase:

x□ Discovery □ Preclinical □ Clinical □ Post-launch

Typical user workflow (describe what the user will do, step by step, to use your tool):

Within the pipeline, this step will be completely automated. Previous user input on population properties and drug binding properties will be passed to FEniCS-pulse. Raw data will automatically be processed and summarized in a report with figures.

Therapeutic area: Test effects of drugs on 3D cardiac conduction and contraction

Documentation:

□ Publication/Validation:

□ Webinar:

□ Other: https://pypi.org/project/fenics-pulse/0.1.3.post1/

Software requirements (scripting language, libraries, tools): …

Simulations will be run in local HPC cluster. The simulations will be quite computationally intensive and depending on the size of the population, could require >100 hours of CPU time and generate ~500 GB of raw data. Platform will serve as interface.

System and computing requirements (operative system, launch batch mode, single-/multi-threading): …

Linux, launch batch mode, multi-threading

Tool Files (number of files, type, format, size, etc.) - files needed to run the model:

Tool summary:

Input parameters: ¨ <5 x 5<X<10 ¨ X>10

Simulation types: ¨ 1 x X>1

Dataset Files (number of files, type, format, etc.) - in case your tool includes a dataset:

Dataset summary:

Size:

Number of variables:

Number of records:

Targeted end-user:

¨ Beginner

x Researcher ¨ Clinician ¨ Regulator ¨ Industry